ACUTE HEMOLYTIC ANEMIA COMPLICATING INFECTIOUS MONONUCLEOSIS: REPORT OF TWO CASES*

By DAVID H. APPELMAN, M.D., and GEORGE B. GORDON, M.D.,
Brooklyn, New York

THE development of acute hemolytic anemia during the course of infectious mononucleosis has only recently been reported.[1-4] Dameshek and Schwartz[5] had previously reported the occurrence of hemolytic anemia in a patient with infectious mononucleosis but in this instance, sulfadiazine had been administered. Ellis, Wollenman and Stetson[1] described the occurrence of acute hemolytic anemia in an illness resembling infectious mononucleosis in which autohemagglutinins, hemolysins and a positive Donath-Landsteiner test were found. In their case the heterophil antibody titer was markedly elevated initially, as were the hemagglutinin titers. Coincident with the fall in the heterophil antibody titer a decrease in serum hemagglutinins was demonstrated. Wilson, Ward and Gray[3] reported a case of infectious mononucleosis and hemolytic anemia. Sawit-

* Received for publication November 4, 1953.
From the Department of Medicine, The Beth-El Hospital, Brooklyn, N. Y.

sky, Papps and Wiener [4] observed another case of acute hemolytic anemia complicating infectious mononucleosis. By the use of the Coombs' reagent, autosensitization of the patient's red cells was demonstrable during the hemolytic phase of the disease.

Case Reports

Case 1. A 21 year old white single male college student was admitted to the Beth-El Hospital on July 21, 1952. He had been ill for two weeks with sore throat, fatigability, weakness, anorexia, fever and enlargement of the cervical glands. Fever had ranged from 100° to 102° F. The past history, apart from measles and mumps in childhood, and family history were noncontributory. The use of drugs or sera prior to admission was denied except for one injection of penicillin and 2 gm. of Aureomycin taken orally during the first week of the illness.

Physical examination on admission disclosed a moderately pale, feverish white male with slightly icteric skin and sclerae. Rectal temperature was 103° F. The pharynx was injected. Numerous easily removable small white plaques were found on the tongue, gums and cheeks. Slightly tender lymph nodes, varying from pea to almond size, were palpated in the posterior cervical, submaxillary and anterior cervical areas. The liver and spleen were not palpable. No other significant findings were noted.

Laboratory: Hemoglobin, 7.6 gm. (55 per cent); red cells, 2.8 million; white cells, 7,000; neutrophils, 25 per cent; eosinophils, 1 per cent; monocytes, 4 per cent; lymphocytes, 70 per cent. Many of these lymphocytes were atypical and characteristic of infectious mononucleosis. Platelets numbered 300,000 per cubic millimeter. Reticulocytes numbered 7 per cent on the third hospital day and 8 per cent one week later. No abnormality in the structure of the red blood cells was noted. The red blood cell fragility test was normal. A sternal marrow aspiration revealed a granulocytic-erythrocytic ratio of 50:50. Megakaryocytes were normal in number, and the granulocytic elements were made up of 30 per cent myelocytes, 15 per cent metamyelocytes, 35 per cent segmented neutrophils and 20 per cent staff neutrophils. An increase in erythroblasts was noted.

The heterophil agglutination test was positive in a dilution of 1:2048. The Davidsohn exclusion test confirmed the diagnosis of infectious mononucleosis. The Coombs' test was negative on two occasions. The urinary urobilinogen was 1:20. No bile was found in the urine. Blood chemical examinations showed an icteric index that ranged from 16.6 to 25.3. The total serum bilirubin varied from 1.14 to 1.8 mg. per 100 c.c., and the direct serum bilirubin from 0.4 to 0.81 mg. per 100 c.c. Total serum proteins were 7.1 gm. per 100 c.c., with an albumin of 3.9 gm. per 100 c.c. and a globulin of 3.2 gm. per 100 c.c. Serum total cholesterol was 127 mg. per cent and the free cholesterol was 94 mg. per cent. The urea nitrogen, sugar, chlorides, sodium, potassium, alkaline phosphatase and carbon dioxide combining power were normal. The cephalin flocculation was 3 plus and the thymol turbidity was 4.5 units.

The electrocardiogram revealed mild myocardial changes which reverted to normal one week later.

Twenty-five milligrams of ACTH were administered intravenously in 500 c.c. of glucose in distilled water daily for five days. Each infusion was given over a 10 hour period. A rapid improvement of the throat lesions, lymphadenopathy and toxicity ensued. However, the icterus and anemia persisted. The patient was discharged from the hospital on August 9, 1952, with a hemoglobin of 60 per cent, 2.9 million erythrocytes and 8 per cent reticulocytes; quantitative serum bilirubin was 1.3 mg. per cent.

Follow-up examinations revealed a gradual rise in hemoglobin and red blood cells, accompanied by decreasing serum bilirubin level and reticulocyte counts. On November 11, 1952 the hemoglobin was 15.6 gm., with a red blood cell count of 5,140,000. Leukocytes were 5,050 per cubic millimeter, of which 49 per cent were segmented neutrophils, 3 per cent staff neutrophils, 46 per cent lymphocytes and 2 per cent eosinophils. The patient was asymptomatic and had returned to full activity.

Comment on Case 1: Following the report of the laboratory findings, it became apparent that the patient had both infectious mononucleosis and hemolytic anemia. The diagnosis of infectious mononucleosis was supported by the lymphadenopathy, positive heterophil agglutination test and the lymphocytosis with atypical lymphoid cells. However, the presence of jaundice, anemia, reticulocytosis and an erythroblastic marrow indicated that hemolytic anemia also existed. Dr. M. Morrison, the hematologist, concluded from peripheral blood and bone marrow studies that this was infectious mononucleosis with hemolytic anemia. It can be assumed that the hemolytic anemia occurred as a complication of the infectious mononucleosis, since the history did not indicate any preëxisting hemolytic disease, and recovery from the hemolytic phase followed subsidence of the infectious mononucleosis.

Case 2. A 22 year old white single male was admitted to the Beth-El Hospital on September 30, 1946. He gave a five week history of weakness, fatigability, sluggishness and "rust-colored" urine. Jaundice and fever appeared in the fourth week of illness. He was hospitalized following a fainting spell. Past history was negative except for an appendectomy in 1943 and furunculosis successfully treated with penicillin while he was in Germany in 1945. No history referable to malaria or other tropical diseases was elicited.

On his admission the patient was slightly asthenic, with icteric skin and sclerae. The pharynx was injected, and small discrete lymph nodes were scattered throughout the neck. The spleen was palpable 4 cm. below the costal margin. Rectal temperature was 103° F. No other significant findings were noted.

Laboratory examinations on the morning following his admission were: hemoglobin, 4.3 gm. (28 per cent); red blood corpuscles, 1.4 million, and 8,800 leukocytes per cubic millimeter. The differential count showed 70 per cent lymphocytes, 28 per cent segmented neutrophils and 2 per cent staff neutrophils. Atypical lymphocytes characteristic of infectious mononucleosis were seen. About 25 per cent of the red blood corpuscles were spherocytic. A marked anisocytosis was present. Reticulocytes numbered 7 per cent. Five normoblasts per 100 white blood cells were found on the blood smear. Platelets numbered 390,000 per cubic millimeter. Bleeding time, coagulation time, clot retraction time and prothrombin time were normal. A sternal marrow aspiration revealed a granulocytic-erythrocytic ratio of 50:50. Megakaryocytes were normal in number, and the granulocytic elements were made up of 35 per cent myelocytes, 35 per cent segmented neutrophils, 10 per cent metamyelocytes and 20 per cent staff neutrophils.

The heterophil agglutination test was positive in a dilution of 1:512. The red blood corpuscle fragility test with hypotonic saline solutions showed initial hemolysis at 0.48 per cent and complete hemolysis at 0.42 per cent. (With normal blood, hemolysis usually begins in the tube containing 0.44 or 0.42 per cent salt solution and is complete in the tube containing 0.34 per cent salt solution.) The urine was strongly positive for urobilinogen. Bile, hemosiderin and hemoglobin were absent from the urine.

Blood chemical examinations showed an icterus index of 15, a delayed van den Bergh reaction and a serum protein of 7.1 gm. per cent. The albumin was 3.9 gm.

per cent and the globulin was 3.2 gm. per cent. Serum total cholesterol was 100 mg. per cent and the cholesterol esters were 125 mg. per cent. The urea nitrogen, sugar and chlorides were normal. The cephalin flocculation test was 3 plus.

The Kline test was negative. Blood cultures showed no organisms. Repeated fecal examinations failed to reveal any parasites or ova. No malarial parasites were found in the bone marrow and peripheral blood specimens. The patient was Rh positive and group "O." Agglutination tests for brucellosis, typhoid, paratyphoid A and B, and typhus fever were negative.

Roentgenologic examination of long bones and chest was normal. The basal metabolic rate was plus 18. Fragility tests done on the blood of the patient's relatives were within normal limits and no cytologic abnormalities were found.

The patient was given 3,500 c.c. of blood during the first week of hospitalization. The hemoglobin rose to 5.5 gm. (36 per cent), with a red blood cell count of 1.9 million. The other hematologic and biochemical examinations were relatively unchanged. The urinary urobilinogen reached a titer of 1:100.

Two weeks after admission of the patient, additional laboratory examinations were done; tests for cold agglutinins, for paroxysmal hemoglobinuria by Mackenzie's modification [6] of the Donath-Landsteiner test, and for Marchiafava's disease by the Ham and Horack [7] procedure were all uniformly negative. The heterophil agglutination test was positive in a dilution of 1:256. The Davidsohn exclusion test confirmed the diagnosis of infectious mononucleosis.

The clinical course during the 10 weeks of hospitalization was uneventful. The temperature returned to normal on the twelfth day, after reaching a peak of 104° F. 48 hours after admission. The lymphadenopathy persisted. The spleen became barely palpable. A slight icteric tint to the skin was still perceptible on discharge.

Laboratory examinations carried out during the last week of hospitalization showed a hemoglobin of 9 gm. (58 per cent), with a red blood cell count of 2.8 million. Leukocytes were 7000 per cubic millimeter, of which 52 per cent were segmented neutrophils, 4 per cent eosinophils, 42 per cent lymphocytes and 2 per cent monocytes. No atypical lymphocytes were seen. A few macrocytes and an occasional spherocyte were seen on the stained blood smear. Reticulocytes were 3 per cent, and the platelets numbered 380,000 per cubic millimeter. Sternal marrow showed a granulocytic-erythrocytic ratio of 60:40. Granulocytic series showed 20 per cent neutrophilic myelocytes, 10 per cent eosinophilic myelocytes, 12 per cent metamyelocytes, 15 per cent staff neutrophils and 5 per cent eosinophils. The icterus index was 17. Quantitative serum bilirubin was 0.8 mg. per cent. The heterophil agglutination test was negative. The red blood cell fragility test had returned to normal. Initial hemolysis began at 0.44 per cent and was completed at 0.32 per cent. The urinary urobilinogen was positive in a dilution of 1:100.

There was nothing in the patient's history prior to the onset of the infectious mononucleosis to indicate a preëxisting hemolytic disease. The subject was not seen again until 18 months after discharge. He looked well and had no icterus, and the spleen was not palpable. Laboratory examinations at this time were: hemoglobin, 15.4 gm. (100 per cent); red blood corpuscles, 4.6 million, and 6,000 leukocytes per cubic millimeter. The differential count showed 51 per cent segmented neutrophils, 10 per cent staff neutrophils, 33 per cent lymphocytes, 5 per cent monocytes and 1 per cent eosinophils. No pathologic cells were seen. Reticulocytes numbered 1.5 per cent, platelets 450,000 per cubic millimeter. Bleeding and coagulation times were normal. The heterophil agglutination test was negative. The red blood corpuscle fragility test with hypotonic salt solution showed initial hemolysis at 0.44 per cent and complete hemolysis at 0.34 per cent. Blood chemical examinations showed an icterus index of 4.3 units, a negative cephalin-cholesterol flocculation test and a zinc

turbidity test of 6.2 units. Bile, hemoglobin and hemosiderin were absent from the urine. The urinary urobilinogen was within normal limits.

Comment on Case 2: The lymphadenopathy, splenomegaly, lymphocytosis with atypical lymphoid cells and the positive heterophil agglutination test confirmed the diagnosis of infectious mononucleosis. The jaundice, anemia, increased red blood cell fragility to hypotonic salt, spherocytosis, increased urinary urobilinogen and erythroblastic marrow revealed that acute hemolytic anemia was also present. There was nothing in the patient's history prior to the onset of the infectious mononucleosis to indicate a preëxisting hemolytic disease. Infectious hepatitis might be considered as a possible diagnosis, but cases of infectious hepatitis almost invariably show an increased resistance to hypotonic saline.

Discussion

Infectious mononucleosis is usually a benign, self-limited disease requiring only symptomatic therapy. However, with the new peak of attention now being enjoyed by this disease, it can no longer be properly regarded as a diagnostic curiosity or as a benign and unimportant disorder. The disease may impair vital organs, frequently incapacitates and occasionally kills. Occasionally, serious complications such as hepatitis, thrombocytopenia, myocarditis, central nervous system involvement and splenic rupture may develop. Several fatal cases have been described, with death due to splenic rupture or to central nervous system involvement.[8, 9] In most patients the leukocyte picture is the only cytologic change of any significance. One of its outstanding features is the lack of anemia. However, a few cases with anemia and/or thrombocytopenia have been reported. Reed and Helwig [10] reported 300 cases of infectious mononucleosis, of which three presented severe anemia associated with a marked reduction of the white blood cells and platelets. The authors considered this pancytopenia to be part of the infectious mononucleosis. The complication of acute hemolytic anemia is rare but does occur.[1-4] The importance of recognizing that hemolytic anemia can occur during the course of infectious mononucleosis lies in its therapeutic implications. A noted hematologist examined the second patient and, after confirming that he had both hemolytic anemia and infectious mononucleosis, wrote that the patient's only hope for recovery lay in splenectomy. The realization that acute hemolytic anemia may occur as a complication of infectious mononucleosis and will disappear coincident with the fall in the heterophil antibody titer makes the consideration of splenectomy unnecessary in such patients.

There is no specific treatment for infectious mononucleosis. ACTH has been reported [11] to be beneficial in seriously ill cases of infectious mononucleosis. Treatment of the first patient with ACTH did result in rapid improvement.

Summary

Acute hemolytic anemia, although rare, does occur as a complication of infectious mononucleosis. Recovery from the hemolytic phase follows recovery from the infectious mononucleosis. Further clinical trial in severe or complicated cases of infectious mononucleosis is necessary to evaluate the specificity as well as the effectiveness of ACTH in the treatment of this disease.

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